



## STATISTICAL ANALYSIS PLAN

**Study Protocol  
Number:** E2007-J081-240

**Study Protocol  
Title:** A multicenter, uncontrolled, open-label study to evaluate the safety and tolerability of intravenous perampanel as substitute for oral tablet in subjects with partial onset seizures (including secondarily generalized seizures) or primary generalized tonic-clonic seizures

**Date:** 14<sup>th</sup> Feb 2020

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMPA	$\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
$\beta$ -hCG	beta-human chorionic gonadotropin
BMI	Body mass index
BUN	blood urea nitrogen
CoA	certificate(s) of analysis
CI	confidence interval
CNS	central nervous system
CPK	creatine phosphokinase
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CT	computed tomography
CYP	cytochrome P450
EAID	enzyme inducing antiepileptic drug
ECG	electrocardiogram
EEG	electroencephalogram
EIAED	enzyme inducing antiepileptic drug
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
EU	European Union
GABA	gamma-aminobutylic acid
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
ILAE	International League Against Epilepsy
IRB	institutional review board

Abbreviation	Term
ITT	intent-to-treat
IUPAC	International Union of Pure and Applied Chemistry
IUS	intrauterine hormone-releasing system
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LLT	lowest level term
LNH	low/normal/high
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
POS	partial onset seizure
PT	preferred term
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
ULN	upper limit of normal
VNS	vagal nerve stimulation
WHO DD	World Health Organization Drug Dictionary

## 1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and statistical methods in detail that will be used to analyze and report results Eisai Protocol E2007-J081-240.

### 1.1 Study Objectives

#### 1.1.1 Primary Objective

To evaluate the safety and tolerability of perampanel administered as a 30-minute intravenous (IV) infusion after switching from oral tablets (8 to 12 mg/day) as an adjunctive therapy in subjects with epilepsy with partial onset seizures (including secondarily generalized seizures) or primary generalized tonic-clonic seizures.

#### 1.1.2 Secondary Objectives

- To evaluate the plasma concentration of perampanel before and after switching from oral tablets to 30-minute IV infusion
- To evaluate the seizure frequency before and after switching from oral tablets to 30-minute IV infusion

### 1.2 Overall Study Design and Plan

This study is a multicenter, uncontrolled, open-label study in subjects with partial onset seizures (including secondarily generalized seizures) or primary generalized tonic-clonic seizures. This study will consist of 3 phases (Pretreatment Phase, Treatment Phase, Follow-up Phase).

#### Pretreatment Phase

During the Pretreatment Phase, subjects will be screened and be assessed for their eligibility to participate in the study. Subject informed consent/assent will be obtained prior to the screening (Day -28 to Day -7), and subsequently protocol eligibility will be established. Eligible subjects must be on a stable dosage (8 to 12 mg/day) of oral perampanel as an adjunctive therapy with up to 3 marketed concomitant antiepileptic drugs (AEDs) for at least



28 days prior to the Treatment Phase. Enrolled subjects will be hospitalized 1 day prior to switching to IV perampanel (Day -1 [Visit 2]).

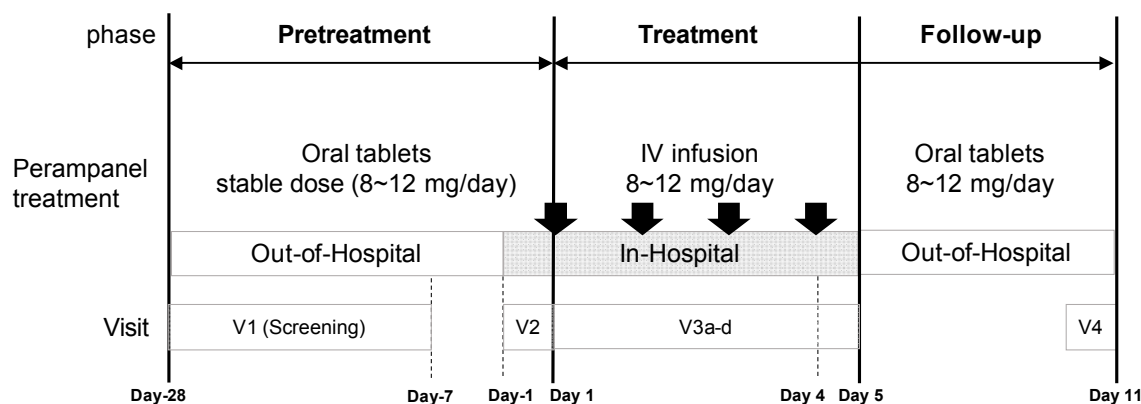
### Treatment Phase

During the Treatment Phase, subjects will be hospitalized, and oral perampanel must be switched to equivalent dose of IV perampanel infusion. Subjects will receive 30-minute IV infusion (once a day) for 4 days. Then, the subject must be switched to oral perampanel at the equivalent daily dose of the IV infusion.

### Follow-up Phase

The assessments at the Follow-up Visit will be performed 7 days (+7 days) after the last IV infusion.

The study design is shown in [Figure 1](#).



**Figure 1. Study Design**

## 2 DETERMINATION OF SAMPLE SIZE

This study is an open label study for safety evaluation of IV perampanel infusion and the sample size (20 subjects) is not based on statistical power considerations, but rather on feasibility. It is considered that it will be a sufficient number of subjects for the safety evaluation of IV perampanel infusion if the sample size is 20.

### 3 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

#### 3.1 Study Endpoints

The safety endpoints are AEs, clinical laboratory tests (biochemistry, hematology, and urinalysis), vital signs, weight, and 12-lead ECG.

The efficacy endpoint is the seizure frequency per day in each of 3 phases (Pretreatment Phase, Treatment Phase, Follow-up Phase). Seizure frequency per day will be derived from the information recorded in the subject diaries.

The pharmacokinetic endpoint is plasma concentration of perampanel.

#### 3.2 Study Subjects

##### 3.2.1 Definitions of Analysis Sets

###### Safety Analysis Set

The Safety Analysis Set is the group of subjects who received at least 1 IV perampanel infusion.

###### Efficacy Analysis Set

The Efficacy Analysis Set is the group of subjects who received at least 1 IV perampanel infusion and had at least 1 postdose efficacy measurement.

###### Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set is the group of subjects who received at least 1 IV perampanel infusion and had at least 1 evaluable measurement of plasma perampanel concentration.

### 3.2.2 Subject Disposition

The number (percentage) of subjects who completed/discontinued the Pretreatment Phase and the number of the reason(s) for the discontinuation will be presented.

For the summary of the subject disposition, the following items will be presented;

- the number of subjects who were treated
- the number (percentage) of subjects who completed/discontinued the Treatment Phase and the number of the primary reason and other reason(s) for the discontinuation
- the number (percentage) of subjects who discontinued the Treatment Phase and assessed at the Follow-up Visit
- the number (percentage) of subjects who completed/discontinued the Follow-up Phase and the number of the primary reason and other reason(s) for the discontinuation
- the number (percentage) of subjects who completed/discontinued the study and the number of the primary reason and other reason(s) for the discontinuation

Subject data listings will be provided.

### 3.2.3 Protocol Deviations

Major protocol deviation criteria will be established and subjects with major protocol deviations will be identified and documented before the database lock. A subject data listing of major protocol deviations will be provided.

### 3.2.4 Demographic and Other Baseline Characteristics

This summary table will be generated on the Safety Analysis Set, Efficacy Analysis Set and Pharmacokinetic Analysis Set (for instance, this will be summarized as “ Safety Analysis Set” if all the analysis set will be the same.).

Continuous demographic and baseline variables include

- Age

- Height
- Weight
- BMI

Categorical demographic and baseline variables include

- Age group (< 18 years, 18 - < 65 years, 65years ≤)
- Sex
- Race
- Ethnicity
- Daily dose of oral Perampanel (8 mg, 10 mg, 12 mg)

Epilepsy specific history and characteristics at study entry will also be summarized by:

- Time since latest diagnosis of epilepsy (months)
- Etiology
- Epileptic syndrome
- Suspected localization of the epileptogenic region
- Seizure type
- Inducer / Non-Inducer
- Number of concomitant AEDs at the Screening (ie., Visit 1)

When summarizing the number of concomitant AEDs at the Screening, Oral Perampanel will not be included.

Subject data listings for demographic and other baseline characteristics will be provided.

### **Medical History**

A subject data listing of medical history and current medical condition will be provided.

### 3.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes.

Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug. If there are medications started after the last dose of study drug, those will be defined as post medications. In addition, prior and concomitant non-pharmacological procedures will be defined similarly to prior, concomitant and post medications.

All medications and non-pharmacological procedures will be presented in subject data listings.

## 3.3 Data Analysis General Considerations

### 3.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

### 3.3.2 Adjustments for Covariates

No adjustment for covariates will be performed.

### 3.3.3 Multiple Comparisons/Multiplicity

No statistical comparison is planned in this study.

### 3.3.4 Examination of Subgroups

The following subgroup will be used for the efficacy and the safety (ie., AE) analyses. See [section 3.4.1](#) and [3.6.2](#).

- Concomitant AED (Inducer/ Non-Inducer)

### 3.3.5 Handling of Missing Data, Dropouts, and Outliers

The details of handling of missing data will be described in [section 6](#).

### 3.3.6 Other Considerations

Not applicable.

## 3.4 Efficacy Analyses

All efficacy analyses will be performed based on the Efficacy Analysis Set. Efficacy data will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, Q1, Q3, maximum for continuous variables; number [percentage] for categorical variables). In the summary table, the following seizure type will be presented separately.

- For subjects who had POS(s) as an epilepsy history, POS total seizures (i.e., sum of the Simple partial seizures without motor signs, Simple partial seizures with motor signs, Complex partial seizures and Complex partial seizures with secondary generalization)
- For subjects who had generalized seizures as an epilepsy history, Tonic-clonic seizures

### 3.4.1 Primary Efficacy Analyses

The seizure frequency per day in each of the corresponding phases (ie., Pretreatment Phase, Treatment Phase, Follow-up Phase) will be summarized using descriptive statistics. The derivation of seizure frequency will be defined in the [section 6.2](#).

The seizure frequency per day from the Pretreatment Phase to the Follow-up Phase for each subject will be displayed using a spaghetti-plot by seizure types (ie., POS total seizures and Tonic-clonic seizures). The plot will also be produced by concomitant AED (Inducer, Non-Inducer). Furthermore, the number of seizures from the Pretreatment Phase to the Follow-up Phase for each subject will be displayed using a spaghetti-plot by POS total seizures and Tonic-clonic seizures.

### 3.4.2 Secondary Efficacy Analyses

No secondary efficacy analyses are planned for this study.

### 3.4.3 Other Efficacy Analyses

No other efficacy analyses are planned for this study.

## 3.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

### 3.5.1 Pharmacokinetic Analyses

The Pharmacokinetic Analysis Set will be used for summaries of perampanel plasma concentrations.

#### 3.5.1.1 Plasma Concentration Analysis

Plasma concentrations of perampanel will be summarized using summary statistics (n, mean, SD, median, min and max) by nominal sampling time points and dose. Maximum plasma concentrations among 0.5, 1, 1.5 hours after oral administration in each individual subject is defined as  $C_{\max, po}$ . Summary statistics of  $C_{\max, po}$  will be also derived.

Plasma concentrations of perampanel which are normalized to dose 8 mg, hereinafter called to as dose-normalized plasma concentrations, will be summarized using summary statistics (n, mean, SD, median, min and max) by nominal sampling time points. Summary statistics of  $C_{\max, po}$  which are normalized to dose 8 mg, hereinafter called to as dose-normalized  $C_{\max, po}$ , will be also derived.

Ratio of plasma concentrations at 0.5 hours after start of intravenous administration on Days 1, 2, 3, 4 to  $C_{\max, po}$  will be calculated and summarized using summary statistics (n, mean, SD, median, min and max).

Spaghetti plot will be developed using individual plasma concentrations of perampanel for Y and time points for X; each for pre-dose (pre-dose concentrations on Day –1 to Day 4) and post-dose (0.5, 1, 1.5 hours after dosing on Day –1 and 0.5 hours after start of intravenous administration on Days 1, 2, 3, 4). The plasma concentrations of 8 mg, 10 mg and 12 mg will be shown in different type of lines.

Spaghetti plot will be developed using individual dose-normalized plasma concentrations of perampanel for Y and time points for X ; each for pre-dose (pre-dose concentrations on Day –

1 to Day 4) and post-dose (0.5, 1, 1.5 hours after dosing on Day –1 and 0.5 hours after start of intravenous administration on Days 1, 2, 3, 4).

Following box plots will be developed;

- Pre-dose concentrations on Day –1 to Day 4 each for 8 mg, 10 mg and 12 mg
- C<sub>max</sub>, po and plasma concentrations at 0.5 hours after start of intravenous administration on Days 1, 2, 3, 4 each for 8 mg, 10 mg and 12 mg
- Dose-normalized pre-dose concentrations on Day –1 to Day 4
- Dose-normalized C<sub>max</sub>, po and dose-normalized plasma concentrations at 0.5 hours after start of intravenous administration on Days 1, 2, 3, 4

Plasma concentrations of perampanel will be listed for each subject belonging to Safety Analysis Set by actual sampling time.

### 3.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable

## 3.6 Safety Analyses

All safety analysis will be performed based on the Safety Analysis Set. Safety data will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; number [percentage] for categorical variables).

### 3.6.1 Extent of Exposure

The parameters for extent of exposure defined as follows will be summarized by study phase (ie., Pre-treatment, Treatment, Follow-up) accordingly.

#### 1. Duration of exposure (days)

- the date of last study drug dosing – the date of first study drug dosing + 1
- the date of last oral perampanel dosing – the date of first oral perampanel dosing + 1  
(for Pretreatment Phase and the Follow-up Phase, respectively)



2. Oral-perampanel mean daily dose (8 to 12 mg) (for Pretreatment Phase and Follow-up Phase, respectively)
    - Sum of daily dose / duration of exposure (days)
  3. IV-perampanel-infusion mean daily dose (mg)
    - Sum of daily dose\* / duration of exposure (days)
- \*: Daily dose: the planned concentration of IV-perampanel (mg/mL) \* the actual IV-perampanel-infusion volume (mL)

Subject data listings will be provided.

### 3.6.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA version 21.1 or later). Adverse events will be coded to the MedDRA lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

A treatment-emergent adverse event (TEAE), defined in [section 6.3](#), will be included in summary tables.

A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT.

An overview table, including the incidence of and the number of subjects with TEAEs, Treatment-related TEAEs, severe TEAEs, serious TEAEs, deaths, other serious TEAEs, and TEAEs that led to treatment discontinuation and interruption will be provided.

All analysis of TEAEs by SOC and PT will also be performed. The incidence of following events will be reported as the number (percentage) of subjects with TEAEs by MedDRA SOC and PT.

- TEAEs
- TEAEs by maximum severity
- Treatment-related TEAEs

- Treatment-related TEAEs by maximum severity

In addition, the incidence of following events will be reported as the number (percentage) of subjects with AEs by MedDRA SOC and PT. If a subject experienced at least 1 AE within a specific SOC and PT in the multiple phases, the subject will be counted once in each phase. Furthermore, the overview table and AE tables by SOC and PT will also be provided for each study phase in one table.

- AEs (non-TEAEs) that occurred during the Pretreatment Phase
- TEAEs that occurred during the Treatment Phase
- TEAEs that occurred during the Follow-up Phase

The following tables will be produced by concomitant AEDs (ie., Inducer, Non-Inducer) and planned perampanel dose.

- TEAEs by SOC and PT
- Treatment-related TEAEs by SOC and PT

Subject data listings of all deaths, serious adverse events (SAEs), AE leading to study treatment discontinuation. All AE regardless of treatment-emergent or not will be included in the subject data listings.

### **AEs of special Interest**

TEAEs which were reported as an event associated with renal dysfunction or an event associated with anaphylaxis on the CRF will be summarized by PT.

### **3.6.3 Laboratory Values**

Laboratory results will be summarized using Système International (SI) units. For all quantitative parameters, the actual value and the change from baseline to each postbaseline visit will be summarized using summary statistics. Qualitative parameters will be summarized by number and percentage of subjects, and changes from baseline to each postbaseline visit will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value is below (L), within (N), or above (H) the laboratory parameter's reference range. The changes from baseline to each postbaseline visit will be reported using shift tables. The result of LNH classification will be provided in a subject data listing.

Sponsor's Grading for Laboratory Values (see [Appendix 1](#)) will be used to identify subjects with Treatment-emergent markedly abnormal laboratory value (TEMAV). The number (percentage) of subjects with TEMAV (markedly abnormal high/low) will be summarized separately for the Treatment Phase and the Follow-up Phase. The TEMAV will be defined in the [section 6.3](#).

The baseline to each postbaseline values for quantitative data will be displayed using Box plot.

Subject data listings will be provided.

### 3.6.4 Vital Signs

Summary statistics for vital signs parameters (diastolic and systolic blood pressure, pulse, respiratory rate, and temperature) and weight, and changes from baseline to each postbaseline visit will be presented.

In addition, clinically notable vital sign values will be identified using the criteria in [Table 1](#). The clinically notable vital sign values will be summarized using frequency count (percentage) separately for the Treatment Phase and the Follow-up Phase.

<b>Table 1. Vital Sign Criteria</b>			
<b>Variable</b>	<b>Criterion value <sup>a</sup></b>	<b>Change relative to baseline <sup>a</sup></b>	<b>Clinically notable range</b>
Pulse	>120 bpm	Increase of $\geq 15$ bpm	H
	<50 bpm	Decrease of $\geq 15$ bpm	L
Systolic BP	>180 mmHg	Increase of $\geq 20$ mmHg	H
	<90 mmHg	Decrease of $\geq 20$ mmHg	L
Diastolic BP	>105 mmHg	Increase of $\geq 15$ mmHg	H
	<50 mmHg	Decrease of $\geq 15$ mmHg	L

<b>Table 1. Vital Sign Criteria</b>			
<b>Variable</b>	<b>Criterion value <sup>a</sup></b>	<b>Change relative to baseline <sup>a</sup></b>	<b>Clinically notable range</b>
Weight	--	Increase of $\geq 7\%$	H
	--	Decrease of $\geq 7\%$	L
Respiratory Rate	>30 bpm	Increase of $\geq 10$ bpm	H
	< 8 bpm	Decrease of $\geq 4$ bpm	L
BP = blood pressure, H = high, L = low. a: Clinically notable means that a value must meet the criterion value and must attain the specified magnitude of change relative to baseline.			

The baseline to each postbaseline visit values will be displayed using Box plot.

Subject data listings will be provided.

### 3.6.5 Electrocardiograms

Shift tables will present changes from baseline to each postbaseline visit in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant).

Subject data listings will be provided.

### 3.6.6 Other Safety Analyses

No other safety analyses are planned for this study.

## 3.7 Other Analyses

No other analyses are planned for this study.

## 4 INTERIM ANALYSES

No interim analyses are planned for this study.

## 5 CHANGES IN THE PLANNED ANALYSES

A summary of all major additions, changes and deletions in the planned analyses described in the protocol will be provided in this section.

- The analysis for AE of special interest was added ([section 3.6.2](#)).
- The analysis for TEAE and Treatment-related TEAE by concomitant AED (Inducer, Non-Inducer) was added ([section 3.6.2](#)).
- The plot for seizure frequency by concomitant AED (Inducer, Non-Inducer) was added ([section 3.4.1](#)).
- The analysis for clinically notable vital sign values was added ([section 3.6.4](#)).

## 6 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

The data will be handled as follows. The sponsor will determine how to handle all data prior to data base lock.

### 6.1 General Data Handling

#### Definition of Baseline data

Baseline is defined as the last non-missing value observed on or prior to the first study drug dispensing date.

#### Definition of Change from Baseline, Percent Change from Baseline

- Change from baseline = Post-baseline value - Baseline value
- % Change from baseline = (Change from baseline / Baseline value) \* 100

For any baseline value of 0, the subject's corresponding percent change from baseline will not be included in the summary statistics table.

#### Handling of data within the follow-up period after discontinuation

Data in the Follow-up Phase obtained after discontinuation will be included in the summary tables. These data will be presented in the subject data listing.

## 6.2 Efficacy Data Handling

### Handling of seizure frequency

- **Baseline (ie., Pretreatment Phase)**

Baseline seizure frequency will be composed of the dispensed diary. Baseline seizure frequency will be calculated as the number of seizures per day (see below). All diary data collected during the Pretreatment Phase (ie., the date of first diary entry to the first dose date of Perampanel IV infusion) will be used in the computation of baseline seizure frequency per day.

$$\frac{\text{Sum of seizures during the Pretreatment Phase}}{\text{Number of study days during the Pretreatment Phase}}$$

Study days during the Pretreatment Phase will be the period between visit 1 and visit 2.

- **Treatment Phase**

Treatment Phase seizure frequency will be composed of the dispensed diary. Treatment Phase seizure frequency will be calculated as the number of seizures per day (see below). All diary data collected during the Treatment Phase (ie., the first dose date of Perampanel IV infusion to the first dose date of oral Perampanel) will be used in the computation of baseline seizure frequency per day.

$$\frac{\text{Sum of seizures during the Treatment Phase}}{\text{Number of study days during the Treatment Phase}}$$

Study days during the Treatment Phase will be the period between visit 3a and the day after visit 3d.

- **Follow-up Phase**

Follow-up Phase seizure frequency will be composed of the dispensed diary. Follow-up Phase seizure frequency will be calculated as the number of seizures per day (see below). All diary data collected during the Follow-up Phase (ie., the first dose date of oral Perampanel to the date of last diary entry) will be used in the computation of baseline seizure frequency per day.

$$\frac{\text{Sum of seizures during the Follow – up Phase}}{\text{Number of study days during the Follow – up Phase}}$$

Study days during the Follow-up Phase will be the period between the day after visit 3d and visit 4.

## **Handling of missing data**

### **Seizure frequency**

If subjects have a missing seizure count in any of each seizure type (ie, simple partial seizure with motor signs, simple partial seizure without motor signs, complex partial seizure, and complex partial seizure with secondarily generalized seizure) for each unique diary record, the overall seizure frequency for that record will be handled as missing data. Similarly, if complex partial seizure and/or complex partial seizure with secondarily generalized seizure are missing for each unique diary record, then complex partial seizure plus secondary generalized seizure frequency will be handled as a missing data.

## **6.3 Safety Data Handling**

### **Definition of derived variables for extent of exposure**

The derivation rule will be presented in the [section 3.6.1](#).

### **Treatment-emergent adverse event**

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during time from the first dose of study drug to 28 days after the subject's last dose, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

### **TEMAV (Treatment-Emergent Markedly Abnormal Value)**

A TEMAV is defined as follows:

- For a phosphate, if the post baseline grade increases from baseline and the post baseline grade is greater than or equal to 3 then a value will be determined to be a TEMAV.
- For all other parameters presented in the section 12, if the post baseline grade increases from baseline and the post baseline grade is greater than or equal to 2 then a value will be determined to be a TEMAV.

If the grade of baseline value is missing, then, if the grade of post-baseline value fall within the above TEMAV definition, the laboratory values will be classified into treatment emergent markedly abnormal. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

#### **Handling of below lower quantification values in laboratory results**

- In the cases where laboratory result contains below lower quantification (BLQ) value, it will be replaced to the lower limit value of quantification (LLOQ) for summary tables.

### **6.4 Pharmacokinetic Data Handling**

#### **6.4.1 Lower Limit of Quantification of Perampanel Plasma Concentration**

The LLOQ of perampanel plasma concentrations is 0.250 ng/mL.

#### **6.4.2 BLQ Handling for Calculation of PK Parameters**

Not applicable

#### **6.4.3 BLQ Handling for Developing Concentration-Time Profiles**

Not applicable

#### **6.4.4 Handling of Anomalous Concentration Values**

The handling of anomalous concentration values will follow the guidance in the Eisai manual 302-104.00-MNL for non compartmental PK analysis (Version Date: 08 Jun 2016).



#### 6.4.5 General Rules for Presentation of Drug Concentrations and PK Parameters

When presenting individual/raw (raw, hereafter) values and summary statistics, the following rule will be applied: for drug concentrations, all summary statistics (mean, median, and standard deviation [SD]) will have 3 significant digits.

Variable	Unit	N	Digit rule	Raw/ Minimum/ Maximum	Mean Media n	SD	Geomet ric Mean	CV (%)
Perampanel concentration	ng/mL	X	Significant digits	3	3	3	-	-

## 7 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

## 8 STATISTICAL SOFTWARE

All statistical analyses will be conducted by the designee, using validated standard programs or double programming. For analyses needed in data review, single programming will be used.

All statistical analyses will be performed using SAS (version 9.2 or later). As necessary, other validated statistical software will also be used.

## 9 MOCK TABLES, LISTINGS, AND GRAPHS

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

## Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	$<LLN - 10.0 \text{ g/dL}$ $<LLN - 100 \text{ g/L}$ $<LLN - 6.2 \text{ mmol/L}$	$<10.0 - 8.0 \text{ g/dL}$ $<100 - 80 \text{ g/L}$ $<6.2 - 4.9 \text{ mmol/L}$	$<8.0 \text{ g/dL}$ $<80 \text{ g/L}$ $<4.9 \text{ mmol/L}$	N/A
Leukocytes (total WBC)	$<LLN - 3.0 \times 10^9/L$ $<LLN - 3000/mm^3$	$<3.0 - 2.0 \times 10^9/L$ $<3000 - 2000/mm^3$	$<2.0 - 1.0 \times 10^9/L$ $<2000 - 1000/mm^3$	$<1.0 \times 10^9/L$ $<1000/mm^3$
Lymphocytes	$<LLN - 800/mm^3$ $<LLN - 0.8 \times 10^9/L$	$<800 - 500/mm^3$ $<0.8 - 0.5 \times 10^9/L$	$<500 - 200/mm^3$ $<0.5 - 0.2 \times 10^9/L$	$<200/mm^3$ $<0.2 \times 10^9/L$
Neutrophils	$<LLN - 1.5 \times 10^9/L$ $<LLN - 1500/mm^3$	$<1.5 - 1.0 \times 10^9/L$ $<1500 - 1000/mm^3$	$<1.0 - 0.5 \times 10^9/L$ $<1000 - 500/mm^3$	$<0.5 \times 10^9/L$ $<500/mm^3$
Platelets	$<LLN - 75.0 \times 10^9/L$ $<LLN - 75,000/mm^3$	$<75.0 - 50.0 \times 10^9/L$ $<75,000 - 50,000/mm^3$	$<50.0 - 25.0 \times 10^9/L$ $<50,000 - 25,000/mm^3$	$<25.0 \times 10^9/L$ $<25,000/mm^3$
METABOLIC/LABORATORY				
Albumin, serum-low (hypoalbuminemia)	$<LLN - 3 \text{ g/dL}$ $<LLN - 30 \text{ g/L}$	$<3 - 2 \text{ g/dL}$ $<30 - 20 \text{ g/L}$	$<2 \text{ g/dL}$ $<20 \text{ g/L}$	N/A
ALP	$>ULN - 3.0 \times ULN$	$>3.0 - 5.0 \times ULN$	$>5.0 - 20.0 \times ULN$	$>20.0 \times ULN$
ALT	$>ULN - 3.0 \times ULN$	$>3.0 - 5.0 \times ULN$	$>5.0 - 20.0 \times ULN$	$>20.0 \times ULN$

	Grade 1	Grade 2	Grade 3	Grade 4
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bicarbonate, serum-low	<LLN – 16 mmol/L	11 – 15 mmol/L	8 – 10 mmol/L	<8 mmol/L
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium corrected, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium corrected, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L	>500 mg/dL; >27.8 mmol/L
Glucose, serum-poglycemia-low (h)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L

	Grade 1	Grade 2	Grade 3	Grade 4
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	N/A	<3.0 – 2.5 mmol/L	<2.5 mmol/L
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L
Uric acid, serum-high (hyperuricemia)	>ULN - 10 mg/dL ≤ULN – 0.59 mmol/L	N/A	N/A	>10 mg/dL >0.59 mmol/L

ALP = alkaline phosphatase, ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT =  $\gamma$ -glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).